In response, Applicants respectfully note that in order to assist in the review of the application method claims 7-12 and 22-25 have been added directed to therapeutic treatment, and method claims 13-18, 26 and 27 have been added directed to preventive treatment. In this manner issues relative to preventive treatment only apply to claims 13-18, 26 and 27, and should not apply to method claims 7-12 and 22-25. Moreover, claims 1 and 5 have been amended to be directed to compounds, and claim 19 has been added to be directed to compounds. Still further the medicament claims have been clarified to be directed to compositions and their use can be preventive and/or therapeutic.

With the above in mind, Applicants respectfully submit that the preventive treatment of microbial infection is enabled whereby one having ordinary skill in the art would be capable of practicing Applicants' invention without undue experimentation.

The presently claimed invention has inhibitory action against drug efflux pumps of microorganisms, especially against that of Pseudomonas aeruginosa (hereinafter abbreviated as P. aeruginosa), as demonstrated in the examples in the specification. In this regard, the Examiner's attention is directed to pages 175-177 of the specification. P. aeruginosa is one of common bacteria which distributes in almost every moist environment and can survive in ordinary conditions. P. aeruginosa, per se, hardly becomes solely a causal bacterium of infectious diseases of healthy people. However, P. aeruginosa has recently been very often isolated from patients with opportunistic infection as nosocomial infection. In particular, patients with degraded immunity, for example, patients in intensive care units with a severe underlying disease such as a burn are susceptible to infection by P. aeruginosa. This has become a serious

clinical problem because of a high mortality of severe infection by P. aeruginosa. From this viewpoint, prevention of formation of P. aeruginosa infection is clinically very important.

For an infection which is suspected to be caused by P. aeruginosa, an empiric therapy before isolation and identification of a causal bacterium is commonly applied with the assumption that the infection is caused by P. aeruginosa, because therapeutic treatments only after identification of P. aeruginosa are sometimes too late to successfully cure the infection. For that purpose, cephalosporins are often used. However, the antibacterial activities of cephalosporins against P. aeruginosa are unsatisfactory. Accordingly, cephalosporins are sometimes administered at a maximum dose or at a dose beyond an ordinary clinical dose. For such type of prophylactic treatment, administration of cephalosporins doses beyond an ordinary dose are not desirable without identification of a causal bacterium from viewpoints of adverse effect, load to a patient, and emergence of resistant mutants. For these reasons, if a medicament is available that can enhance activities of antibacterial agents and prevent bacteria from acquiring resistance in preventive treatment of an infection, such medicament is obviously expected to be highly effective for various kinds of infectious diseases.

As clearly explained in the specification, the presently claimed invention can act on a bacterium, with acquired resistance to an antimicrobial agent, to inhibit its drug efflux pump and prevent defluxion of an antibacterial agent, thereby increasing an intrabacterial concentration of the antibacterial agent to significantly enhance its antibacterial action to the bacterium. This action of the claimed invention can successfully prevent the formation of infection with the aid of enhanced antibacterial action of the antibacterial agent used in combination. Thus, the

examiner's attention is directed to the indication that the action of the claimed medicament is to enhance an antibacterial action of an antibacterial agent, and on the basis of this action, one of ordinary skill in the art would readily understand that the claimed medicament can prevent formation of a bacterial infection in combination with an antibacterial agent, because every kind of antibacterial agent inherently has preventive action of formation of infection based on its antibacterial activity. Moreover, as explained in the specification, the claimed medicament also prevents formation of resistance of bacteria to antibacterial agents, and can eliminate already acquired resistance from resistant bacteria. These actions can also successfully serve as preventive nature of the claimed invention.

Accordingly, one having ordinary skill in the are would be capable of practicing Applicants' invention without undue experimentation as a preventive treatment, whereby the rejection of record should be withdrawn.

Response To Rejection Under 35 U.S.C. 112, Second Paragraph

In response to the rejection of claim 5 under 35 U.S.C. 112, second paragraph, Applicants respectfully submit that claim 5 has been amended herein to even more clearly recite Applicants' invention. In this regard, claim 5 has been amended to explicitly include the definition of the recited variables. Accordingly, this ground of rejection should be withdrawn.

Reponse to Rejection Under 35 U.S.C. 102(b)

Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by NISHIGAKI et al. (Chem. Pharm. Bull. 1975). In this ground of rejection, the Examiner notes that the document may be unclear, and in fact the document is very difficult to read. However, the Examiner has submitted a Chemical Abstract with the document and refers to compound RN 58492-31-2.

In response, Applicants submit herewith a clear copy of NISHIGAKI et al.

Moreover, Applicants note that claim 5 has been amended to recite that X represents C-H and Y represents C-H or nitrogen atom. Still further, claim 19 has been added which maintains the original recitation for X, but recites Z_{1-4} in R^{14} as being an alkyl group having 1, 3, or 4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms. Accordingly, NISHIGAKI et al. does not teach or suggest the compounds as recited in claims 5 and 19, the medicament compositions as recited in dependent claims 20 and 21, nor the methods as recited in dependent claims 22-27. Therefore, the rejection of record is no longer applicable, and should be withdrawn.

Response To Indicated Possible Objection Under 37 C.F.R. 1.75

The Office Action has advised that if claim 1 is found to be allowable, claims 2-4 would be objected to under 37 C.F.R. § 1.75 as being substantial duplicates thereof.

In response, Applicants note that as pointed out in the section of the MPEP referred to in the Office Action, i.e., MPEP 706.03(k), Applicants have a right to express their invention in a reasonable number of ways. Applicants respectfully submit that their claims are not duplicative.

In the instant application, Applicants express their invention is a reasonable number of ways, and commensurate with the scope of protection in the originally filed application. If the Examiner deems that any changes to the claims are desirable, the Examiner is respectfully requested to contact the undersigned by telephone to discussed the same.

CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notice of Allowance and allowability is therefore respectfully requested.

Should the Examiner have any further comments or questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
Kiyoshi NAKAYAMA et al.

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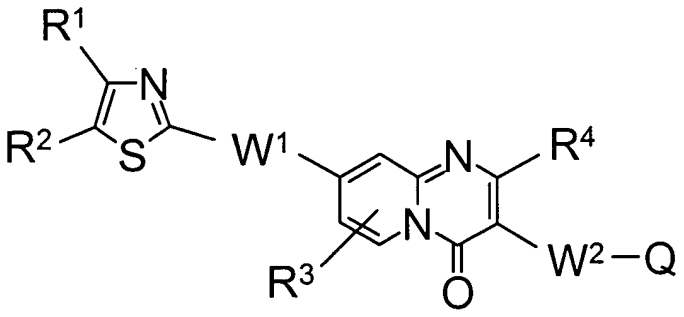
APPENDIX
MARKED-UP COPY OF AMENDED CLAIMS 1-5

1. (Amended) A [medicament for preventive and/or therapeutic treatment of a microbial infection, which comprises as an active ingredient a] compound represented by the following [general] formula (I) or a physiologically acceptable salt thereof, or a hydrate thereof:



wherein, R^1 and R^2 each independently represent hydrogen atom, a halogen atom, hydroxyl group, a group of OZ_{1-6} (the group of OZ_{1-6} represents an alkyl group having 1-6 carbon atoms or a fluoroalkyl group having 1-6 carbon atoms, which bonds via the oxygen atom), a group of $S(O)_nZ_{1-4}$ (Z_{1-4} represents an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms or an alkylene group derived therefrom), a group of $N(R^{12})(R^{13})$ (R^{12} and R^{13} each independently represent hydrogen atom, an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms), a group of Z_{1-8} which may be substituted (Z_{1-8} represents an alkyl group having 1-8 carbon atoms or a fluoroalkyl group having 1-8 carbon atoms), a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group, or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group,

heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of OZ_{1-4}, a group of $S(O)_nZ_{1-4}$, a group of $N(R^{12})(R^{13})$, a group of Z_{1-4}, carboxyl group, a group of CO_2Z_{1-4}, group of $CONH_2$, a group of $CONH(Z_{1-4})$ and a group of $CON(Z_{1-4})(Z_{1-4})$);

W^1 represents a group selected from the group consisting of -CH=CH-, $-N(R^{12})CO-$, $-CON(R^{12})-$, $-CH_2O-$ and $-CH_2CH_2-$ (each of the aforementioned groups binds to the thiazole ring at the left end);

R^3 represents hydrogen atom, a halogen atom, hydroxyl group or an amino group;

R^4 represents a group selected from the group consisting of hydrogen atom, a group of $-OZ_{0-4}R^5$ (Z_{0-4} represents an alkylene group having 1-4 carbon atoms, a fluorine-substituted alkylene group having 1-4 carbon atoms or a single bond, and R^5 represents a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of OZ_{1-4}, a group of $S(O)_nZ_{1-4}$, a group of $N(R^{12})(R^{13})$, a group of Z_{1-4}, carboxyl group, a group of CO_2Z_{1-4}, group of $CONH_2$, a group of $CONH(Z_{1-4})$ and a group of $CON(Z_{1-4})(Z_{1-4})$), a group of $-S(O)_nZ_{0-4}R^5$, a group of $-N(R^6)(R^7)$ {R^6 and R^7 each independently represent hydrogen atom or Z_{1-4}, or they may bind to each other to form a saturated or unsaturated 5- to 7-membered ring (the ring may contain one or two hetero atoms as ring constituting atoms), and R^6 and R^7 may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of $OCON(R^{12})(R^{13})$, a group of

$CON(R^{12})(R^{13})$, a group of $N(R^{12})CON(R^{12})(R^{13})$, a group of Z_{1-4}, a group of OZ_{1-4}, a group $S(O)_nZ_{1-4}$, group of CH_2OH, a group of $(CH_2)_mN(R^{12})(R^{13})$, carboxyl group, cyano group, a group of $CO\text{-}Z_{1-4}(R^{10})\text{-}N(R^{12})(R^{13})$ (R^{10} is a substituent corresponding to a side chain on an amino acid carbon or a group of $-Z_{1-4}-R^{11}$ (R^{11} represents a substituent which forms a quaternary salt) and a group of $CO\text{-}Z_{1-4}\text{-}N(R^{12})(R^{13})$ with $(CH_2)q$ }, a 5- or 6-membered aryl group which may be substituted and a 5- or 6-membered unsaturated heterocyclic group which may be substituted;

W^2 represents a single bond or $-C(R^8)=C(R^9)-$ (R^8 and R^9 each independently represent hydrogen atom, a halogen atom, a lower alkyl group, an alkoxy group, cyano group, carboxyl group, hydroxymethyl group, cyanomethyl group, vinyl group or a group of $N(R^{12})(R^{13})$), Q represents an acidic group, and W^2 and Q may bind together to form vinylidenethiazolidinedione in *E*- or *Z*-configuration or an equivalent heterocyclic ring;

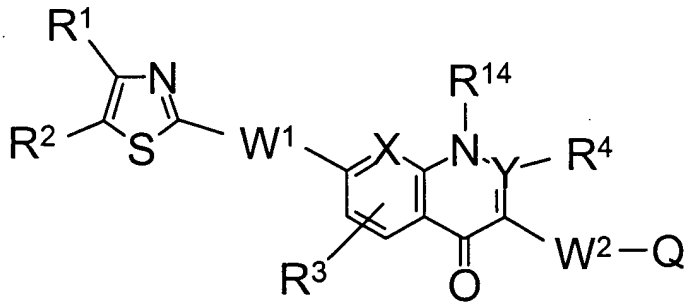
m and n each independently represent an integer of 0 to 2, and q represents an integer of 0 to 3.

2. (Amended) A medicament composition for eliminating resistance of a microorganism with acquired drug resistance, which comprises [the] a compound represented by [the aforementioned general] formula (I) according to claim 1 or a physiologically acceptable salt thereof as an active ingredient.

3. (Amended) A medicament composition for enhancing effect of an antimicrobial agent, which comprises a compound represented by [the aforementioned general] formula (I) according to claim 1 or a physiologically acceptable salt thereof as an active ingredient.

4. (Amended) A pharmaceutical composition for preventive and/or therapeutic treatment of a microbial infection, which comprises a compound represented by [the aforementioned general] formula (I) according to claim 1 or a physiologically acceptable salt thereof together with an antimicrobial agent.

5. (Amended) A [medicament for preventive and/or therapeutic treatment of a microbial infection, which comprises as an active ingredient a] compound represented by the following [general] formula (I) or a physiologically acceptable salt thereof, or [hydrates] hydrate thereof



[wherein, R^1, R^2, R^3, R^4, W^1, W^2 and Q have the same meanings as those defined above;] wherein, R^1 and R^2 each independently represent hydrogen atom, a halogen atom, hydroxyl group, a group of $OZ_{1\text{-}6}$ (the group of $OZ_{1\text{-}6}$ represents an alkyl group having 1-6 carbon atoms or a fluoroalkyl group having 1-6 carbon atoms, which bonds via the oxygen atom), a group of $S(O)_nZ_{1\text{-}4}$ ($Z_{1\text{-}4}$ represents an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms or an alkylene group derived therefrom), a group of $N(R^{12})(R^{13})$ (R^{12} and R^{13}

each independently represent hydrogen atom, an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms), a group of Z_{1-8} which may be substituted (Z_{1-8} represents an alkyl group having 1-8 carbon atoms or a fluoroalkyl group having 1-8 carbon atoms), a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group, or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of OZ_{1-4}, a group of $S(O)_nZ_{1-4}$, a group of $N(R^{12})(R^{13})$, a group of Z_{1-4}, carboxyl group, a group of CO_2Z_{1-4}, group of $CONH_2$, a group of $CONH(Z_{1-4})$ and a group of $CON(Z_{1-4})(Z_{1-4})$);

W^1 represents a group selected from the group consisting of -CH=CH-, $-N(R^{12})CO-$, $-CON(R^{12})-$, $-CH_2O-$ and $-CH_2CH_2-$ (each of the aforementioned groups binds to the thiazole ring at the left end);

R^3 represents hydrogen atom, a halogen atom, hydroxyl group or an amino group;

R^4 represents a group selected from the group consisting of hydrogen atom, a group of $-OZ_{0-4}R^5$ (Z_{0-4} represents an alkylene group having 1-4 carbon atoms, a fluorine-substituted alkylene group having 1-4 carbon atoms or a single bond, and R^5 represents a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of OZ_{1-4}, a group of $S(O)_nZ_{1-4}$, a group of $N(R^{12})(R^{13})$, a group of Z_{1-4}, carboxyl group, a group of CO_2Z_{1-4}, group of $CONH_2$, a group of $CONH(Z_{1-4})$ and a group of

$CON(Z_{1-4})(Z_{1-4})$), a group of $-S(O)_nZ_{0-4}R^5$, a group of $-N(R^6)(R^7)$ {R^6 and R^7 each independently represent hydrogen atom or Z_{1-4}, or they may bind to each other to form a saturated or unsaturated 5- to 7-membered ring (the ring may contain one or two hetero atoms as ring constituting atoms), and R^6 and R^7 may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of $OCON(R^{12})(R^{13})$, a group of $CON(R^{12})(R^{13})$, a group of $N(R^{12})CON(R^{12})(R^{13})$, a group of Z_{1-4}, a group of OZ_{1-4}, a group $S(O)_nZ_{1-4}$, group of CH_2OH, a group of $(CH_2)_mN(R^{12})(R^{13})$, carboxyl group, cyano group, a group of $CO\text{-}Z_{1-4}(R^{10})\text{-}N(R^{12})(R^{13})$ (R^{10} is a substituent corresponding to a side chain on an amino acid carbon or a group of $-Z_{1-4}\text{-}R^{11}$ (R^{11} represents a substituent which forms a quaternary salt) and a group of $CO\text{-}Z_{1-4}\text{-}N(R^{12})(R^{13})$ with $(CH_2)q$ }, a 5- or 6-membered aryl group which may be substituted and a 5- or 6-membered unsaturated heterocyclic group which may be substituted;

W^2 represents a single bond or $-C(R^8)=C(R^9)-$ (R^8 and R^9 each independently represent hydrogen atom, a halogen atom, a lower alkyl group, an alkoxy group, cyano group, carboxyl group, hydroxymethyl group, cyanomethyl group, vinyl group or a group of $N(R^{12})(R^{13})$), Q represents an acidic group, and W^2 and Q may bind together to form vinylidenethiazolidinedione in *E*- or *Z*-configuration or an equivalent heterocyclic ring; m and n each independently represent an integer of 0 to 2, and q represents an integer of 0 to 3; R^{14} represents hydrogen atom, Z_{1-4}, $Z_{1-4}R^5$ or $Z_{1-4}OR^5$; and X represents C-H and Y [each independently represent] represents C-H or nitrogen atom.